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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,858	07/23/2001	Kazuo Kubo	049441-0127	1181

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EXAMINER

BERCH, MARK L

ART UNIT	PAPER NUMBER
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1624

DATE MAILED: 05/15/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application N .

09/889,858

Applicant(s)

KUBO ET AL.

Examiner

Mark L. Berch

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-52 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-52 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All   b) ☐ Some \*   c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                  | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). ____.  |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                         | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>6</u> . | 6) <input type="checkbox"/> Other: .  |

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#### DETAILED ACTION

The previous Lack of Unity requirement erroneously assigned claims 48-52 (part) to just Group III, when this should have been assigned to all three groups.

Claims 1-52 are rejected as being drawn to an improper Markush Group. The claims are drawn to multiple inventions for reasons set forth in the above requirement for restriction. This does not constitute an art recognized genus. The claims are examined only to the extent that they read on the elected invention. Cancellation of the non-elected subject matter (limitation to quinazolines) will overcome the rejection.

#### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-15, 50-2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. "Heterocyclic" is indefinite. What is the size of the ring? What is the number and nature of the heteroatoms? Can the ring be fused or spiroconnected to another ring, and if so, what kind of ring? Can the ring be bridged? Unsaturated? Cf. *In re Wiggins*, 179 USPQ 421, 423.

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2. The term “other” at fourth from last line of claims 1 and 5 is ambiguous. It could mean “a different” or it could mean “another”, neither of which fits well. Replacement with “a” is suggested.
3. The inclusion of Kaposi’s sarcoma in claim 50-1 appears to be double inclusion, already covered by “tumor”, unless applicants are using some unusual definition of a tumor.
4. “Use of” is not a permitted format for US patent claims and is indefinite (In re Fong, 129 USPQ 264; Ex parte Erlich, 3 USPQ2d 1011). (Claim 50).
5. What role does “target” play in claim 52? What is the difference between an ordinary blood vessel and a “target blood vessel”?

Claims 50-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for other disorders, does not reasonably provide enablement for tumors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claim sets forth the treatment of cancer generally, except for leukemias, since nearly all cancers are tumors. However, there never has been a compound capable of treating cancer generally. There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from

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a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task.

When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs Novo Nordisk*, 42 USPQ2nd 1001, 1006.

Further, "tumor" covers more than just cancers. It also covers many neoplasms, cancerous or not. A neoplasm is any abnormal tissue that grows by cellular proliferation more rapidly than normal, or continues to grow after the stimulus that initiated the new growth has ceased, or shows lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such a term also covers precancerous conditions such as lumps, lesions, and polyps. In addition, "tumor" covers things other than neoplasms. It also covers any kind of swelling arising from inflammation. Thus, the claim would cover treatment of many kinds of inflammation. The specification cannot support that.

Claims 1-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for other forms, does not reasonably provide

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enablement for solvates. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims are drawn to solvates. But the scores of examples presented all failed to produce a solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." Hence, applicants must show that solvates can be made, or limit the claims accordingly.

*Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-52 are rejected under 35 U.S.C. 102(a) as being anticipated by JP

11158149.

The reference has a publication date of June 15, 1999, prior to the 1/20/2000 date.

Applicant cannot rely upon the foreign priority papers to overcome this rejection

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because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Applicants are requested to state whether there are US applications corresponding to WO 200147890 or JP 11158149.

Claims 1-2,4-7, 14, 48-52 are rejected under 35 U.S.C. 102(b) as being anticipated by 6,143,764.

The reference is the equivalent of WO 97/17329; the US equivalent is used for convenience; the PCT publication date of May 15, 1997 is relied on.

Note the following, all of which anticipate:

Example 153 N-[4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]phenyl]-N'-(2-methoxyphenyl)urea [113]

Example 154 N-[4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]phenyl]-N'-(3-methoxyphenyl)urea [114]

Example 155 N-[4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]phenyl]-N'-(4-methoxyphenyl)urea [99]

Example 156 N-[4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]phenyl]-N'-(2-fluorophenyl)urea [116]

Example 157 N-(4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]phenyl)-N'-n-butylurea [220]

These correspond to  $R^2 = R^3 = \text{methoxy}$ ,  $R^{11} = \text{substituted phenyl or butyl}$ , all others = H. The same utilities are seen, note e.g. claim 44, 45.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 3, 8-13, 16-18, 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over 6,143,764.

Note the above anticipation rejection. Claims 3, 15 are homologues, having an extra methyl group on the urea nitrogen. Such a feature is taught in the definition of R5 at column 5, line 46, and is exemplified in compound 201 in column 35. Also, such a variation is considered obvious because of the close structural similarity. See *In re Hoeksema*, 154 USPQ 169; *Ex parte Weston*, 121 USPQ 428; *Ex parte Bluestone*, 135 USPQ 199; *In re Doebl*, 174 USPQ 158.

Claims 8-9, 13, 16-18 claim the phenylene group with halogens present. This is taught by the reference at column 3, line 2. Similarly, claims 12-13, 16-18 have the alkoxy substituent, show in the same line.

Claims 10-11 are homologues, having an extra methyl group or two on a carbon of the phenylene. This is taught by the reference at column 3, line 2. Also, compounds that differ only by the presence or absence of an extra methyl group or two are homologues. Homologues are of such close structural similarity that the disclosure of a compound renders *prima facie* obvious its homologue. As was stated in *In re Grose*, 201 USPQ 57, 63, "The known structural relationship between adjacent homologues, for example, supplies a chemical theory upon which a *prima facie* case of obviousness of a compound may rest." The homologue is expected to be preparable by the same method and to have generally the same properties. This expectation is then deemed the motivation for preparing homologues. Of course, these presumptions are rebuttable by the showing of unexpected effects, but initially, the homologues are obvious even in the absence of a specific teaching to add or remove methyl groups. See *In re Wood*, 199 USPQ 137; *In re Hoke*, 195 USPQ 148; *In re Lohr*, 137 USPQ 548; *In re Magerlein*, 202 USPQ 473; *In re Wiechert*, 152 USPQ 249; *Ex parte Henkel*, 130 USPQ 474; *Ex Parte*



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*Fischer* 96 USPQ 345; *In re Fauque*, 121 USPQ 425; *In re Druey*, 138 USPQ 39. In all of these cases, the close structural similarity between two compounds differing by one or two methyl groups was itself sufficient show obviousness. See also MPEP 2144.09, second paragraph.

With regard to claim 47, species 62 is obvious. It has an extra Cl which is obvious for reasons set forth above, and has propyl in stead of butyl. However, the reference teaches alkyl of any size in the definition of A, and in fact a propyl urea is seen in e.g. compound 194 on column 19.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 703-308-4718. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 308-4716. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 708-308-1235.



Mark L. Berch  
Primary Examiner  
Art Unit 1624

May 9, 2002